

CLAIMS

1. The use, as a specific marker for the beta cells of pancreatic islets of Langerhans, of at least one isolated polynucleotide or of the 5 corresponding protein, chosen from:

- the polynucleotides comprising or having one of the following sequences: (a) the sequence SEQ ID NO. 1, (b) a fragment of the sequence SEQ ID NO. 1 of at least 15 consecutive nucleotides, (c) a sequence 10 exhibiting a percentage identity of at least 80%, after optimal alignment, with one of the sequences defined in (a) or in (b), and (d) a sense or antisense sequence complementary to one of the sequences defined in (a), (b) or (c), and

15 - the proteins encoded by the polynucleotides as defined in (a), (b), (c) or (d) above, comprising or having one of the following sequences: (e) the sequence SEQ ID NO. 2, (f) a fragment of the sequence SEQ ID NO. 2 of at least 15 consecutive amino acids, (g) a 20 sequence exhibiting a percentage identity of at least 60%, after optimal alignment, with one of the sequences defined in (e) or in (f) or at least 65% similarity, preferably 80% identity or at least 90% similarity, or even more preferably 90% identity or at least 95% 25 similarity.

2. The use as claimed in claim 1, characterized in that said isolated polynucleotide as defined in (c) is a polynucleotide that is a variant of the sequence SEQ ID NO. 1, comprising a mutation which 30 results in a modification of the amino acid sequence of the protein encoded by the sequence SEQ ID NO. 1.

3. The use as claimed in claim 1, characterized in that said isolated polynucleotide as defined in (b) or in (d) is chosen from the pair of 35 primers SEQ ID NO. 3 and SEQ ID NO. 4 and the pair of primers SEQ ID NO. 5 and SEQ ID NO. 6.

4. The use as claimed in claim 1, characterized in that said isolated polynucleotide can

be obtained by amplification using the pair of primers as defined in claim 3.

5. The use as claimed in claim 1, characterized in that said polynucleotide as defined in (d) is a small interfering RNA (siRNA) which, by interaction with the mRNAs corresponding to said polynucleotide, will bring about their degradation.

10. The use as claimed in claim 1, characterized in that said protein as defined in (g) is a variant of the sequence SEQ ID NO. 2, that has a mutation associated with diabetes or with hyperinsulinism.

15. The use as claimed in claim 1, characterized in that said fragment as defined in (f) has a sequence chosen from the sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10.

8. An isolated polynucleotide as defined in claim 1, characterized in that it comprises or has a sequence chosen from:

20. (a) the sequence SEQ ID NO. 1,

(b) a fragment of the sequence SEQ ID NO. 1 of at least 15 consecutive nucleotides, with the exception of the fragments of at least 15 consecutive nucleotides included in the sequences having the 25 accession numbers, in the NCBI database, No. AX526723, No. AX526725 and No. AX526727,

(c) a sequence exhibiting a percentage identity of at least 80%, after optimal alignment, with one of the sequences defined in (a) or in (b), and

30. (d) a sense or antisense sequence complementary to one of the sequences defined in (a), (b), (c) or (d),

with the exception of the ESTs having the accession numbers, in the GenBank database, BM565129, BM310003,

35. BM875526, BG655918, BQ417284, BQ267316, BU072134, BQ267526, BQ270198, BU581447, BU070173, BQ631692 and BU949895, and also of the sequences having the accession numbers, in the NCBI database, AX526723, AX526725 and AX526727.

9. A probe for detecting, identifying or assaying nucleic acids corresponding to the polynucleotides as defined in claim 1, characterized in that it consists of a polynucleotide as claimed in 5 claim 8.

10. A pair of primers for amplifying nucleic acids corresponding to the polynucleotides as defined in claim 1, characterized in that it is chosen from the pairs of primers as defined in claim 3.

11. A polynucleotide that can be obtained by amplification using the primers as claimed in claim 10.

12. The polynucleotide as claimed in claim 8 or claim 11, characterized in that it is a small interfering RNA corresponding to the polynucleotide as 15 defined in claim 1, which, by interaction with the mRNAs corresponding to said polynucleotide, will bring about their degradation.

13. A method for determining the transcription profile of the gene corresponding to the 20 polynucleotide as claimed in claim 8 or claim 11, or an alteration of said profile, in a biological sample, comprising a first step consisting in obtaining, by any appropriate means, the RNAs from the biological sample, a second step consisting in bringing said RNAs into 25 contact with a labeled probe consisting of a polynucleotide as claimed in any one of claims 8, 9 or 11, under conditions appropriate for hybridization between the RNAs and the probe, and a third step consisting in revealing, by any appropriate means, the 30 hybrids formed.

14. The method as claimed in claim 13, in which the second step is a step consisting of reverse transcription and/or of amplification of the transcripts, carried out using a pair of primers as 35 claimed in claim 10, and the third step is a step consisting in revealing, by any appropriate means, the amplified nucleic acids.

15. The method as claimed in either one of claims 13 or 14, characterized in that it also

comprises a step consisting in evaluating the level of transcription of the gene by comparison with a control selected beforehand.

16. A method for demonstrating the gene
5 corresponding to the polynucleotide as claimed in
claim 8 or claim 11 or the allelic variants of said
gene or a functional alteration of this gene, in a
biological sample, comprising a first step consisting
10 in obtaining, by any appropriate means, the DNA from
the biological sample, a second step consisting in
bringing said DNAs into contact with a labeled probe
consisting of a polynucleotide as claimed in any one of
claims 8, 9 or 11, under conditions appropriate for
15 hybridization between the DNAs and the probe, and a
third step consisting in revealing, by any appropriate
means, the hybrids formed.

17. The method as claimed in claim 16, in
which the second step is an amplification step carried
out using a pair of primers as claimed in claim 10 and
20 the third step is a step consisting in revealing, by
any appropriate means, the amplified nucleic acids
formed.

18. The method as claimed in either one of
claims 16 or 17, characterized in that it also
25 comprises a step consisting in isolating and sequencing
the nucleic acids demonstrated.

19. A kit of reagents for carrying out the
methods as claimed in any one of claims 13 to 18,
comprising:

30 a) at least one probe as claimed in claim 9
and/or one pair of primers as claimed in claim 10;

 b) the reagents required for carrying out a
hybridization reaction between said probe and/or said
primers and the nucleic acid of the biological sample;

35 c) the reagents required for carrying out
an amplification reaction;

 d) the reagents required for detecting
and/or assaying the hybrid formed between said probe
and the nucleic acid of the biological sample, or the

amplified nucleic acids formed.

20. A DNA chip comprising at least one polynucleotide as claimed in claim 8 or claim 11.

5 21. The use of a polynucleotide as claimed in claim 8 or claim 11, for preparing a DNA chip.

22. The use, *in vitro*, of the polynucleotide as claimed in any one of claims 8, 11 or 12, as a means for studying:

10 a) the overexpression of the transporter encoded by the polynucleotide as claimed in claim 8 or claim 11 in model cell lines and the impact on insulin secretion in response to a stimulation with glucose;

15 b) the sensitivity of the cells to cell death (apoptosis) induced by conditions of oxidative stress or of low or high zinc concentration;

c) the steps of differentiation of stem cells into insulin-secreting cells in response to various exogenous stimulations.

20 23. An isolated protein, characterized in that it is encoded by a polynucleotide as claimed in either of claims 8 or 11.

25 24. The protein as claimed in claim 23, characterized in that it comprises or has the sequence SEQ ID NO. 2.

25 25. A fragment of the protein as claimed in claim 24, characterized in that it is chosen from the sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10.

30 26. A protein chip comprising at least one protein or one protein fragment as claimed in any one of claims 23 to 25.

27. The use of a protein or of a protein fragment as claimed in any one of claims 23 to 25, for preparing a protein chip.

35 28. The use of a protein or of a protein fragment as claimed in any one of claims 23 to 25 or of a protein chip as claimed in claim 26, for detecting the presence of antibodies directed against said protein in the serum of an individual.

29. The use of a protein as claimed in any one of claims 16 to 18, for measurements by means of immunochemical and immunoenzymatic methods, or for the search for autoantibodies directed against said protein.

30. A cloning and/or expression vector, characterized in that it comprises an insert consisting of a polynucleotide as claimed in any one of claims 8, 11 or 12.

31. A cell modified with a polynucleotide as claimed in any one of claims 8, 11 or 12 or a vector as claimed in claim 30.

32. A non-human transgenic organism, characterized in that all or some of its cells contain a polynucleotide as claimed in any one of claims 8, 11 or 12 or a vector as claimed in claim 30, in a free or integrated form.

33. The use of a modified cell as claimed in claim 31 or of a non-human transgenic organism as claimed in claim 32, for producing a protein or a protein fragment as defined in any one of claims 23 to 25.

34. A method for preparing a protein or a protein fragment as claimed in any one of claims 23 to 25, characterized in that it comprises culturing modified cells as claimed in claim 31, in particular mammalian cells, or cells from non-human transgenic organisms as defined in claim 32, under conditions that allow the expression of said protein, and purifying said recombinant protein.

35. A monoclonal or polyclonal antibody, characterized in that it is capable of specifically recognizing a protein or a protein fragment as claimed in any one of claims 23 to 25.

36. A protein chip comprising at least one antibody as claimed in claim 35.

37. The use of an antibody as claimed in claim 35, for preparing a protein chip.

38. The use of an antibody as claimed in

claim 35 or of a chip as claimed in claim 36, for detecting and/or purifying a protein or a protein fragment as claimed in any one of claims 23 to 25.

5 39. A method for detecting any protein or protein fragment of claims 23 to 25, in a biological sample, comprising a first step consisting in bringing the biological sample into contact with an antibody as claimed in claim 35, and a second step consisting in demonstrating, by any appropriate means, the antigen-
10 antibody complex formed.

40. A kit for carrying out the method as claimed in claim 39, comprising:

15 a) a monoclonal or polyclonal antibody as claimed in claim 35;
b) the reagents for detecting the antigen-
antibody complex produced during the immunoreaction.

41. The use of an antibody as claimed in claim 35, for detecting and/or sorting islets of Langerhans or else beta cells.

20 42. The use of an antibody as claimed in claim 35 for analyzing the differentiation of stem cells into pancreatic islet cells, preferably into beta cells.

25 43. A method for selecting the beta cells of islets of Langerhans, comprising a first step consisting in bringing the cells of a biological sample liable to contain such islets and/or cells into contact with an antibody as claimed in claim 35, a second step consisting in demonstrating, by any appropriate means, the cells labeled with the antibody, and a third step consisting in isolating, by any appropriate means, the labeled cells.

35 44. A method for analyzing the differentiation of stem cells into pancreatic islet cells or into beta cells, comprising a step consisting in bringing the cells of a biological sample liable to contain said stem cells undergoing differentiation into contact with an antibody as claimed in claim 35, a second step consisting in demonstrating, by any

appropriate means, the cells labeled with the antibody, and a third step consisting in visualizing, by any appropriate means, the labeled cells.

45. The method as claimed in claim 44, also 5 comprising an additional step consisting in isolating, by any appropriate means, the labeled cells.

46. A method of screening for a chemical or biochemical compound that can directly or indirectly interact, *in vitro* or *in vivo*, with the polynucleotide 10 as claimed in either one of claims 8 or 11, characterized in that it comprises a first step consisting in bringing a candidate chemical or biochemical compound into contact with the polynucleotide as claimed in either one of claims 8 15 or 11 or a cell as claimed in claim 31 or a non-human transgenic organism as claimed in claim 32 or a DNA chip as claimed in claim 20, and a second step consisting in detecting the complex formed between the candidate chemical or biochemical compound and the 20 polynucleotide or the cell or the non-human transgenic organism or the DNA chip.

47. A method of screening for a chemical or biochemical compound that can directly or indirectly modulate, *in vitro* or *in vivo*, the expression of the 25 polynucleotide as claimed in either one of claims 8 or 11, characterized in that it comprises a first step consisting in bringing a candidate chemical or biochemical compound into contact with a polynucleotide as claimed in either one of claims 8 or 11 or a cell as 30 claimed in claim 31 or a non-human transgenic organism as claimed in claim 32 or a DNA chip as claimed in claim 20, and a second step consisting in measuring, by any appropriate means, the expression of the polynucleotide as claimed in either one of claims 8 or 35 11.

48. A method of screening for a chemical or biochemical compound that can directly or indirectly interact, *in vitro* or *in vivo*, with the protein or the protein fragment as claimed in any one of claims 23 to

25, characterized in that it comprises a first step consisting in bringing a candidate chemical or biochemical compound into contact with a protein or a protein fragment as claimed in any one of claims 23
5 to 25 or a cell as claimed in claim 31 or a non-human transgenic organism as claimed in claim 32 or a protein chip as claimed in claim 36, and a second step consisting in detecting the complex formed between the candidate chemical or biochemical compound and the
10 protein or the cell or the transgenic organism or the protein chip.

49. A method of screening for a chemical or biochemical compound that can directly or indirectly modulate, *in vitro* or *in vivo*, the expression and/or
15 the activity of the protein as claimed in either one of claims 23 or 24, characterized in that it comprises a first step consisting in bringing a candidate chemical or biochemical compound into contact with a protein or a protein fragment as claimed in any one of claims 23
20 to 25 or a cell as claimed in claim 31 or a non-human transgenic organism as claimed in claim 32 or a protein chip as claimed in claim 36, and a second step consisting in measuring, by any appropriate means, the expression and/or the activity of said protein.

25 50. A medicinal product comprising a product chosen from the polynucleotide as claimed in any one of claims 8, 11 or 12, the protein or the protein fragment as claimed in any one of claims 23 to 25, the antibody as claimed in claim 35, the vector as claimed in
30 claim 30 and the modified cell as claimed in claim 31.

51. The use of a product chosen from: the polynucleotide as claimed in any one of claims 8, 11 or 12, the protein or the protein fragment as claimed in any one of claims 23 to 25, the antibody as claimed
35 in claim 35, the vector as claimed in claim 30 and the modified cell as claimed in claim 31, for preparing a medicinal product intended for the prevention and/or the treatment of diabetes, particularly that associated with the presence of at least one mutation of the gene

corresponding to SEQ ID NO. 1, and/or with abnormal expression of the protein corresponding to SEQ ID NO. 2, or intended for the prevention and/or the treatment of hyperinsulinisms when abnormal expression, 5 maturation or secretion with respect to the insulin gene is observed, or intended to regulate the maturation and/or secretion of insulin in the beta cells or in cells that are to be modified for the purpose of insulin secretion, or intended to regulate 10 beta cell apoptosis phenomena.

52. The use of a product chosen from: the polynucleotide as claimed in any one of claims 8, 11 and 12, the protein or the protein fragment as claimed 15 in any one of claims 23 to 25 and the antibody as claimed in claim 35, for determining an allelic variability, a mutation, a deletion, a loss of heterozygosity or any anomaly of the gene encoding said protein.